

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
7 October 2004 (07.10.2004)

PCT

(10) International Publication Number  
**WO 2004/084895 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 31/4415**,  
31/4355, 31/675, A61P 39/00

(21) International Application Number:  
PCT/IB2004/000899

(22) International Filing Date: 25 March 2004 (25.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/458,167 27 March 2003 (27.03.2003) US

(71) Applicant (for all designated States except US): **MEDICURE, INC.** [CA/CA]; 4-1200 Waverly Street, Winnipeg, Manitoba R3T 0P4 (CA).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **FRIESEN, Albert, David** [CA/CA]; 77 Shorecrest Drive, Winnipeg, Manitoba (CA).

(74) Agents: **DUBUC, J. et al.**; Goudreau Gage Dubuc, Stock Exchange Tower, Suite 3400, 800 Place Victoria, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
2 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATION OF CELL DEATH

(57) Abstract: A method of modulating cell death includes administering pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues, or pharmaceutical compositions thereof.

WO 2004/084895 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/000899

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4415 A61K31/4355 A61K31/675 A61P39/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/57863 A (UNIV MANITOBA ; MEDICURE INC (CA)) 5 October 2000 (2000-10-05) abstract; claims 9-14; tables 10-13 -----	1
X	WO 01/03682 A (MEDICURE INC) 18 January 2001 (2001-01-18) abstract; claims 1-72; examples 1-10 -----	1
X	EP 0 282 696 A (SPECK ULRICH) 21 September 1988 (1988-09-21) abstract column 4, line 45 - column 6, line 29; claims 1-6 ----- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

5 August 2004

Date of mailing of the international search report

29. 09. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/000899

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 339 085 B1 (HAQUE WASIMUL ET AL) 15 January 2002 (2002-01-15) abstract column 4, line 53 - column 5, line 56 column 6, line 36 - column 10, line 32 column 11, line 48 - column 12, line 2; claims 31,56; examples 2-9 -----	1
X	WO 98/32429 A (GALLAGHER JAMES ANTHONY ; UNIV LIVERPOOL (GB); BOWLER WAYNE BARRY (GB)) 30 July 1998 (1998-07-30) abstract; claims 1,6,12 -----	1
X	DATABASE WPI Section Ch, Week 199425 Derwent Publications Ltd., London, GB; Class B05, AN 1994-207332 XP002291398 & SU 1 808 326 A1 (RYAZAN MED INST) 15 April 1993 (1993-04-15) abstract -----	1
X	WO 01/64692 A (MEDICURE INTERNAT INC) 7 September 2001 (2001-09-07) abstract page 1, line 29 - page 5, line 9; claims 40,99,160,219; examples 1-28 -----	1
X	WO 00/53606 A (MEDICURE INC) 14 September 2000 (2000-09-14) abstract page 3, line 11 - page 5, line 30 page 8, lines 1-4 page 18, lines 2-13; claims 50,107; examples 1-9 -----	1
X	GENG M Y ET AL: "Protective effects of pyridoxal phosphate against glucose deprivation-induced damage in cultured hippocampal neurons." JOURNAL OF NEUROCHEMISTRY. JUN 1997, vol. 68, no. 6, June 1997 (1997-06), pages 2500-2506, XP001197371 ISSN: 0022-3042 the whole document ----- -/--	1

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2004/000899

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SAWAKI, SHUNJI ET AL: "Effect of pyridoxal            phosphate administration on hepatitis C            virus RNA in patients with hepatitis type            C"            XP002291396            retrieved from STN            Database accession no. 1997:732628            abstract            &amp; IGAKU TO SEIBUTSUGAKU , 135(4), 149-151            CODEN: IGSBAL; ISSN: 0019-1604, 1997,            XP008033478</p>	1
X	<p>-----            DATABASE CHEMABS [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SAWAKI, SHUNJI ET AL: "Effect of pyridoxal            phosphate on the CD4, CD8 T cell and            HCV-RNA in patients with hepatitis type C"            XP002291397            retrieved from STN            Database accession no. 1998:406378            abstract            &amp; IGAKU TO SEIBUTSUGAKU , 136(5), 143-145            CODEN: IGSBAL; ISSN: 0019-1604, 1998,            XP008033477</p>	1
X	<p>-----            DATABASE WPI            Section Ch, Week 199748            Derwent Publications Ltd., London, GB;            Class B03, AN 1997-516155            XP002291399            &amp; JP 09 221425 A (TAIHO PHARM CO LTD)            26 August 1997 (1997-08-26)            abstract</p>	1
X	<p>-----            YAMASHIMA, T. ET AL: "Neuroprotective            effects of pyridoxal phosphate and            pyridoxal against ischemia in monkeys"            NUTRITIONAL NEUROSCIENCE , 4(5), 389-397            CODEN: NNINFE; ISSN: 1028-415X, 2001,            XP008033483            abstract</p>	1
X	<p>-----            EP 0 379 936 A (VESTA MED PTY LTD)            1 August 1990 (1990-08-01)            abstract            page 3, lines 44-56            page 9, lines 45-55            page 10, line 26 - page 12, line 45; claim            9; example 4            -----            -/--</p>	1

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/000899

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ISHAQUE A ET AL: "Role of vitamins in determining apoptosis and extent of suppression by bcl-2 during hybridoma cell culture"</p> <p>APOPTOSIS, vol. 7, no. 3, June 2002 (2002-06), pages 231-239, XP008033442 ISSN: 1360-8185 the whole document</p> <p>-----</p>	1
P,X	<p>NAMAZI, M. R.: "Pyridoxal 5'-phosphate as a novel weapon against autoimmunity and transplant rejection"</p> <p>FASEB JOURNAL , 17(15), 2184-2186 CODEN: FAJOEC; ISSN: 0892-6638, 2003, XP008033485 the whole document</p> <p>-----</p>	1

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2004/000899

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 1 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim: 1 (partially)

Use of pyridoxal-5'-phosphate for modulating cell death.  
---

2. claim: 1 (partially)

Use of pyridoxic acid for modulating cell death.  
---

3. claim: 1 (partially)

Use of pyridoxal for modulating cell death.  
---

4. claim: 1 (partially)

Use of pyridoxine for modulating cell death.  
---

5. claim: 1 (partially)

Use of pyridoxamine for modulating cell death.  
---

6. claims: 2-10

Use of a compound of the formula of claim 2 for modulating cell death.  
---

7. claims: 11-25

Use of a compound of the formula of claim 11 for modulating cell death.  
---

8. claims: 26-33

Use of a compound of the formula of claim 26 for modulating cell death.  
---

9. claims: 34-40

Use of a compound of the formula of claim 34 for modulating cell death.  
---

10. claims: 41-49

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of a compound of the formula of claim 49 for modulating  
cell death.

---



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/000899

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0057863	A	05-10-2000	US 6043259 A	28-03-2000
			AT 259643 T	15-03-2004
			AU 3314700 A	16-10-2000
			BR 0009292 A	26-12-2001
			CA 2368775 A1	05-10-2000
			DE 60008352 D1	25-03-2004
			DK 1162980 T3	14-06-2004
			EP 1162980 A2	19-12-2001
			WO 0057863 A2	05-10-2000
			JP 2002540144 T	26-11-2002
			NZ 514767 A	27-02-2004
			PT 1162980 T	30-06-2004
WO 0103682	A	18-01-2001	AU 5840200 A	30-01-2001
			CA 2376029 A1	18-01-2001
			EP 1196171 A2	17-04-2002
			WO 0103682 A2	18-01-2001
			US 2003008847 A1	09-01-2003
			US 6489345 B1	03-12-2002
EP 0282696	A	21-09-1988	DE 3705549 A1	01-09-1988
			AT 82125 T	15-11-1992
			CA 1340246 C	15-12-1998
			DE 3875760 D1	17-12-1992
			DK 55888 A	19-08-1988
			EG 18335 A	30-09-1992
			EP 0282696 A2	21-09-1988
			ES 2052609 T3	16-07-1994
			GR 3006693 T3	30-06-1993
			HU 47850 A2	28-04-1989
			JP 2005061 C	11-01-1996
			JP 7010777 B	08-02-1995
			JP 63203621 A	23-08-1988
			JP 2588686 B2	05-03-1997
			JP 7238020 A	12-09-1995
			KR 9509094 B1	14-08-1995
			US 6066659 A	23-05-2000
			US 5288716 A	22-02-1994
			ZA 8800577 A	28-07-1988
US 6339085	B1	15-01-2002	US 2003195236 A1	16-10-2003
			US 2001031770 A1	18-10-2001
			AU 763464 B2	24-07-2003
			AU 3183400 A	28-09-2000
			BR 0008857 A	18-12-2001
			CA 2366602 A1	14-09-2000
			EP 1169322 A1	09-01-2002
			WO 0053606 A1	14-09-2000
			JP 2002539127 T	19-11-2002
			NZ 514567 A	26-11-2002
WO 9832429	A	30-07-1998	AU 5674798 A	18-08-1998
			WO 9832429 A2	30-07-1998
SU 1808326	A1	15-04-1993	NONE	
WO 0164692	A	07-09-2001	AU 3718501 A	12-09-2001
			WO 0164692 A1	07-09-2001

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/000899

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0164692	A		CA 2401655 A1	07-09-2001
			EP 1268498 A1	02-01-2003
			JP 2003525303 T	26-08-2003
			US 2003114677 A1	19-06-2003
			US 2003114678 A1	19-06-2003
			US 2003120074 A1	26-06-2003
			US 2003181422 A1	25-09-2003
			US 2004171588 A1	02-09-2004
			US 2002010158 A1	24-01-2002
WO 0053606	A	14-09-2000	AU 763464 B2	24-07-2003
			AU 3183400 A	28-09-2000
			BR 0008857 A	18-12-2001
			CA 2366602 A1	14-09-2000
			EP 1169322 A1	09-01-2002
			WO 0053606 A1	14-09-2000
			JP 2002539127 T	19-11-2002
			NZ 514567 A	26-11-2002
			US 2003195236 A1	16-10-2003
			US 6339085 B1	15-01-2002
			US 2001031770 A1	18-10-2001
JP 9221425	A	26-08-1997	NONE	
EP 0379936	A	01-08-1990	EP 0379936 A2	01-08-1990
			JP 2237921 A	20-09-1990
			US 5631271 A	20-05-1997
			US 5254572 A	19-10-1993
			ZA 9000319 A	25-09-1991